

5

CLAIMS

1. A formulation comprising molecular arrangements capable of penetrating pores in a barrier, owing to penetrant adaptability, despite the fact that the average diameter of said pores is smaller than the average penetrant diameter, provided that the penetrants can transport agents or else enable agent permeation through the pores after penetrants have entered pores,
- characterised in that** the formulation comprises at least one consistency builder in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Nm/s so that spreading over, and retention at, the application area is enabled and/or at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100 % per 6 months and/or at least one microbicide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphylococcus aureus*, after a period of 4 days.
2. Formulation according to claim 1,
- characterised in that** said at least one consistency builder is added in an amount that increases the formulation viscosity to up to 1 Nm/s and more preferably to up to 0.2 Nm/s.
3. Formulation according to claim 1 or 2,
- characterised in that** said at least one antioxidant is added in an amount that reduces the increase of oxidation index to less than 100 % per 12 months and more preferably to less than 50 % per 12 months.

- 44 -

5
4. Formulation according to any one of the preceding claims,
characterised in that said at least one microbicide is added in an amount that reduces
the bacterial count of 1 million germs added per g of total mass of the formulation to
less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-
bacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphilococcus*
10 *aureus*, after a period of 3 days, and more preferably after a period of 1 day.

5
5. Formulation according to any of the preceding claims,
characterised in that the consistency builder is selected from pharmaceutically
acceptable hydrophilic polymers, such as partially etherified cellulose derivatives,
15 comprising carboxymethyl -, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or
methyl-cellulose; completely synthetic hydrophilic polymers comprising polyacrylates ,
polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-,
poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate,
polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide,
20 polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols,
poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers,
polyaspartamide, (hydrazine cross-linked) hyaluronic acid, silicone; natural gums
comprising alginates, carrageenan, guar-gum, gelatine, tragacanth, (amidated) pectin,
xanthan, chitosan collagen, agarose; mixtures and further derivatives or co-polymers
25 thereof and/or other pharmaceutically, or at least biologically, acceptable polymers.

6. Formulation according to claim 5,
characterised in that the polymer weight fractions are in the range between 0.05 % and
10%, more preferably are in the range between 0.1% and 5 %, even more preferably are
30 in the range between 0.25 % and 3.5 % and most preferably are in the range between 0.5
% and 2 %.

- 5 7. Formulation according to any one of the preceding claims,
characterised in that the anti-oxidant is selected from synthetic phenolic antioxidants,
such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-
butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119,
BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-
10 hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (diphenylamine, p-
alkylthio-o-anisidine, ethylenediamine derivatives, carbazol, tetrahydroindenoindol);
phenols and phenolic acids (guaiacol, hydroquinone, vanillin, gallic acids and their
esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid , salicylic acid,
nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols
15 (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (e.g. -
acetate, -laurate, myristate, -palmitate, -oleate, -linoleate, etc., or an y other suitable
tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide and
thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-
alkylascorbic acids, ascorbyl esters (e.g. 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or
20 linoleoyl-L-ascorbic acid, etc.); non-steroidal anti-inflammatory agents (NSAIDs), such
as indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone,
oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene,
piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine,
chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen);
25 aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics
(amiodarone, aprindine, asocainol), ambroxol, tamoxifene, b-hydroxytamoxifene;
calcium antagonists (nifedipine, nisoldipine, nimodipine, nicardipine, nilvadipine), beta-
receptor blockers (atenolol, propranolol, nebivolol); sodium bisulphite, sodium
metabisulphite, thiourea; chellating agents, such as EDTA, GDTA, desferral;
30 miscellaneous endogenous defence systems, such as transferrin, lactoferrin, ferritin,
cearuloplasmin, haptoglobin, haemopexin, albumin, glucose, ubiquinol-10); enzymatic

- 46 -

5 antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (flavones, flavonols, flavonones, flavanonals, chalcones, anthocyanins), N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamic acids and their esters (coumaric
10 acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice extracts (e.g. from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulfoxides, tetraalkylthiuram disulphides; phytic acid,
15 steroid derivatives (e.g. U74006F); tryptophan metabolites (e.g. 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides.

8. Formulation according to claim 7, \

characterised in that the concentration of BHA or BHT is between 0.001 and 2 w-%, more preferably is between 0.0025 and 0.2 w-%, and most preferably is between 0.005
20 and 0.02 w-%, of TBHQ and PG is between 0.001 and 2 w-%, more preferably is between 0.005 and 0.2 w-%, and most preferably is between 0.01 and 0.02 w-%, of tocopherols is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.075 w-%, of ascorbic acid esters is between
25 0.001 and 5, more preferably is between 0.005 and 0.5, and most preferably is between 0.01 and 0.15 w-%, of ascorbic acid is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.1 w-%, of sodium bisulphite or sodium metabisulphite is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01-0.15 w-%, of thiourea is
30 between 0.0001 and 2 w-%, more preferably is between 0.0005 and 0.2, and most preferably is between 0.001-0.01 w-%, most typically 0.005 w-%, of cysteine is

- 47 -

5 between 0.01 and 5, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1 and 1.0 w-%, most typically 0.5 w-%, of monothioglycerol is between 0.01 and 5 w-%, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1-1.0 w-%, most typically 0.5 w-%, of NDGA is between 0.0005-2 w-%, more preferably is between 0.001-0.2 w-%, and most preferably is between 0.005-0.02 w-%,
10 most typically 0.01 w-%, of glutathione is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.2 w-%, most typically 0.1 w-%, of EDTA is between 0.001 and 5 w-%, even more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.2 w-%, most typically between 0.05 and 0.975 w-%, of citric acid is between 0.001 and 5 w-%, even
15 more preferably is between 0.005 and 3 w-%, and most preferably is between 0.01-0.2, most typically between 0.3 and 2 w-%.

9. Formulation according to any one of the preceding claims,
characterised in that the microbicide is selected from short chain alcohols, comprising
20 ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol, hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xlenol, dichlorophene, hexachlorophene, povidon-iodine; parabenes, especially alkyl-parabenes, such as methyl-, ethyl-, propyl-, or butyl-paraben, benzyl paraben; acids, such as sorbic acid, benzoic acid and their salts;
25 quaternary ammonium compounds, such as alkonium salts, e.g. a bromide, benzalkonium salts, such as a chloride or a bromide, cetrimonium salts, e.g. a bromide, phenoalkecinium salts, such as phenododecinium bromide, cetylpyridinium chloride and other salts; mercurial compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, or any antibioticly active compounds of
30 biological origin, or any mixture thereof.

- 48 -

5 10. Formulation according to claim 9,
characterised in that the bulk concentration of short chain alcohols in the case of ethyl,
propyl, butyl or benzyl alcohol is up to 10 w%, more preferably is up to 5 w-%, and
most preferably is in the range between 0.5-3 w-%, in the case of chlorobutanol is in the
range between 0.3-0.6 w-%; bulk concentration of parabens, especially in the case of
10 methyl paraben is in the range between 0.05-0.2 w-%, and in the case of propyl paraben
is in the range between 0.002 - 0.02 w-%; bulk concentration of sorbic acid is in the
range between 0.05-0.2 w-%, and in the case of benzoic acid is in the range between
0.1-0.5 w-%; bulk concentration of phenols, triclosan, is in the range between 0.1-0.3
w-%, and bulk concentration of chlorhexidine is in the range between 0.01-0.05 w-%.

15 11. Formulation comprising molecular arrangements capable of penetrating
pores in a barrier, owing to penetrant adaptability, despite the fact that the average
diameter of said pores is smaller than the average penetrant diameter, provided that the
penetrants can transport agents or else enable agent permeation through the pores after
20 said penetrants have entered said pores, the agents associated with said penetrants being
glucocorticoids or mineralocorticosteroids (corticosteroids),
characterised in that the relative content of corticosteroids is above 0.1 weight-%,
relative to total dry mass of the formulation.

25 12. Formulation according to claim 11,
characterised in that at least one consistency builder and/or at least one anti-oxidant
and/or at least one microbicide according to any one of the claims 1 through to 10 is
added to the formulation.

30

5

13. Formulation according to claim 11 or 12,

characterised in that the corticosteroid is selected from alclonetasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone, betamethasone 17-valerate, betamethasone 17,21-divalate, betamethasone 21-acetate, betamethasone 21-buytrate, betamethasone 21-propionate, betamethasone 21-valerate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, cortisolone, corticosterone, cortisone, cortisone 17-acetate, 21-deoxybetamethasone, 21-deoxybetamethasone 17-propionate, deoxycorticosterone, desonide, desoxymethasone, dexamethasone, diflorasone diacetate, diflucortolone valerate, flucilorolone acetonide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, 9-alpha-fluorocortisone, 9-alpha-fluorohydrocortisone, 9-alpha-fluoroprednisolone, fluprednidene acetate, flurandrenolone, halcinonide, hydrocortisone, hydrocortisone 17-acetate, hydrocortisone 17-butyrate, hydrocortisone 17-propionate, hydrocortisone 17-valerate, hydrocortisone 21-acetate, hydrocortisone 21-butyrate, hydrocortisone 21-propionate, hydrocortisone 21-valerate, 17-alpha-hydroxyprogesterone, methylprednisolone acetate, mometasone furoate, prednisolone, prednisone, prednisone 17-acetate, prednisone 17-valerate, progesterone, triamcinolone, triamcinolone acetonide.

25

14. Formulation according to any one of the preceding claims,

characterised in that the penetrants are suspended or dispersed in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, provided that said at least two substances differ by at least a factor of 10 in solubility in said liquid or else that said substances when in the form of homo-aggregates, for the more soluble substance, or of hetero-aggregates, for any

30

- 50 -

5 combination of both said substances, have a preferred average diameter smaller than the diameter of the homo-aggregates containing merely the less soluble substance; or else provided that the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating in the vicinity of thermal energy.

10 15. Formulation according to claim 14,
characterised in that the more soluble substance tends to solubilise the droplet and the content of such substance is up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet, whichever is higher.

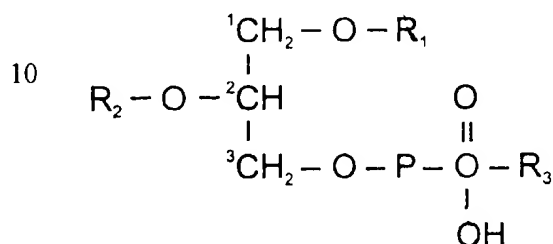
15 16. Formulation according to claim 15,
characterised in that the content of the more soluble substance is below 50 %, especially below 40 % and most preferably below 30 %, of said solubilising concentration of said substance.

20 17. Formulation according to claim 15,
characterised in that the content of the more soluble substance is below 80 %, preferably below 65 % and most preferably below 50 % of said saturation concentration of said substance in the droplet.

25 18. Formulation according to any one of claims 14 to 17,
characterised in that the less soluble amongst the aggregating substances is a lipid or lipid-like material, especially a polar lipid, whereas the substance which is more soluble in the suspending liquid and which increases the droplet adaptability belongs to surfactants or else has surfactant-like properties.

30

- 5 19. Formulation according to claim 18,
characterised in that the lipid or lipid-like material is a lipid or a lipoid from a
 biological source or a corresponding synthetic lipid or any of its modifications, said
 lipid preferably belonging to the class of pure phospholipids with the chemical formula



- where R_1 and R_2 is an aliphatic chain, typically a C_{10-20} -acyl, or -alkyl or partly
 15 unsaturated fatty acid residue, in particular, an oleoyl-, palmitoeloyl-, elaidoyl-, linoleyl-,
 linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or
 stearoyl chain; and where R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl,
 C_{1-4} -alkyl, C_{1-5} -alkyl substituted with carboxy, C_{2-5} -alkyl substituted with hydroxy, C_{2-5} -
 alkyl substituted with carboxy and hydroxy, or C_{2-5} -alkyl substituted with carboxy and
 20 amino, inositol, sphingosine, or salts of said substances, said lipid comprising also
 glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-
 containing lipids, or any other bilayer-forming lipids, in particular half-protonated fluid
 fatty acids, said lipid is selected from the group comprising phosphatidylcholines,
 phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols, phosphatidic
 25 acids, phosphatidylserines, sphingomyelins or other sphingophospholipids,
 glycosphingolipids (including cerebroside, ceramidepolyhexosides, sulphatides,
 sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in
 particular with corresponding sphingosine derivatives, or any other glycolipids, whereby
 two similar or different chains can be ester-groups-linked to the backbone (as in diacyl
 30 and dialkenoyl compound) or be attached to the backbone with ether bonds, as in
 dialkyl-lipids.

- 5 20. Formulation according to claim 18,
characterised in that the surfactant or surfactant-like material is a nonionic, a
zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an
alkyl-tri/di/methyl-ammonium salt, an alkylsulphate salt, a monovalent salt of cholate,
deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, etc.,
10 an acyl- or alkanoyl-dimethyl-aminoxide, esp. a dodecyl- dimethyl-aminoxide, an alkyl-
or alkanoyl-N-methylglucamide, N-alkyl-N,N- dimethylglycine, 3-
(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethylene-
glycol-octylphenyl ether, esp. a nonaethylene-glycol-octylphenyl ether, a polyethylene-
acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a
15 octaethylene-glycol-isotridecyl ether, polyethylene-acyl ether, esp. octaethylenedodecyl
ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-
monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a
polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene-lauryl, -myristoyl, -
cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -
20 lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-
8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a
sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or
alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide,
an alkyl-sulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium
25 glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium
elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-
octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -
phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-phosphatidic acid, -
phosphorylglycerol, or -phosphorylserine, n-tetradecyl- glycero-phosphatidic acid, -
30 phosphorylglycerol, or -phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-,

- 53 -

5 vaccenyl-lysophospholipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

21. Formulation according to any one of claims 14 to 20,
characterised in that the average penetrant diameter is between 30 nm and 500 nm,
10 preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and most preferably between 60 nm and 150 nm.

22. Formulation according to any one of claims 14 to 20,
15 characterised in that the average diameter of the penetrant is 2 to 25 times bigger than the average diameter of the pores in the barrier, preferably between 2.25 and 15 times bigger, even more preferably between 2.5 and 8 times bigger and most preferably between 3 and 6 times bigger than said average pore diameter.

20 23. Formulation according to any one of claims 14 through to 22, characterised in that the dry weight of all carrier droplets in a formulation for the use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total formulation mass, in particular between 0.1 w-% and 30 w-%, particularly preferably between 0.5 w-% and 20 w-%, and most preferably between 1 w-% and 10 w-%.

25 24. Formulation according to any one of claims 14 through to 22, characterised in that the dry weight of all carrier droplets in a formulation for the use on human or animal mucosa is 0.0001 w-% to 30 w-% of total formulation mass.

30

- 54 -

5 25. Formulation according to any one of the claims 1 through to 24,
characterised in that the pH of carrier suspension is between 4 and 10, preferably
between 5 and 9, and even more often up to 8.5, as required to maximise the stability of
formulation.

10 26. A method for preparing a formulation for non-invasive application in
vivo, according to any one of the preceding claims,
characterised in that penetrants capable of associating and/or incorporating said agent
molecules are formed from at least one amphiphilic substance, at least one polar fluid, at
least one edge-active substance or surfactant, at least one corticosteroid in an amount of
15 more than 0.1 w-% based on total dry mass of the formulation, and, in case, other
customary ingredients, which together form said formulation.

20 27. The method of claim 26,
characterised in that at least one edge-active substance or surfactant, at least one
amphiphilic substance, at least one hydrophilic fluid and the agent are dissolved to form
a solution and, if required, are mixed separately, the resulting (partial) mixtures or
solutions then being combined to subsequently induce, preferably by action of
mechanical energy, such as shaking, stirring, vibrating, homogenising, ultrasonication,
shear, freezing and thawing, or filtration using convenient driving pressure, the
25 formation of penetrants that associate with and/or incorporate the agent.

30 28. The method of claims 26 or 27,
characterised in that said amphiphilic substances are either used as such, or dissolved
in a physiologically compatible polar fluid, which may be water or miscible with water,
or in a solvation-mediating agent, together with a polar solution.

- 55 -

- 5 29. The method of claims 26 or 27,
characterised in that said amphiphilic substances are dissolved in highly volatile alcohols, in especially ethanol, or in pharmaceutically acceptable organic solvents, which are then removed, esp. by evaporation, prior to making final preparation.
- 10 30. The method as claimed in claims 28 or 29,
characterised in that the polar solution contains at least one edge-active substance or surfactant.
- 15 31. The method according to any one of claims 26 through to 30,
characterised in that the formation of said penetrants is induced by the addition of required substances into a fluid phase, evaporation from a reverse phase, by injection or dialysis, if necessary under the influence of mechanical stress, such as shaking, stirring, in especially high velocity stirring, vibrating, homogenising, ultrasonication, shearing, freezing and thawing, or filtration using convenient, in especially low (1 MPa) or
20 intermediate (up to 10 MPa), driving pressure.
- 25 32. The method of claim 31,
characterised in that the formation of said penetrants is induced by filtration, the filtering material having pores sizes between 0.01 μm and 0.8 μm , preferably between 0.02 μm and 0.3 μm , and most preferably between 0.05 μm and 0.15 μm , whereby several filters may be used sequentially or in parallel.
- 30 33. The method according to any one of claims 26 through to 32,
characterised in that said agents and penetrants are made to associate, at least partly, after the formation of said penetrants, e.g. after injecting a solution of the drug in a pharmaceutically acceptable fluid, such as ethanol, 1-and 2-propanol, benzyl alcohol,

- 56 -

5 propylene glycol, polyethylene glycol (molecular weight: 200 – 400 D) or glycerol into
the suspending medium, said penetrants being formed previously, using the
corresponding or some other suitable manufacturing method, or simultaneously with the
drug injection, if required using a co-solution of the drug and, at least some, penetrant
ingredients.

10

34. The method according to any one of the claims 26 through to 33,
characterised in that said penetrants, with which the agent molecules are associated
and/or into which the agent is incorporated, are prepared just before the application of
the formulation, if convenient from a suitable concentrate or a lyophilisate.

15

35. Formulation according to any one of claims 11 through to 25,
characterised in that the content of corticosteroids is between 0.1 w-% and 20 w-%,
more preferably between 0.25 w-% and 10 w-% and even more preferably between 0.5
w-% and 5 w-%, relative to total dry mass of drug-loaded carriers.

20

36. Formulation according to claim 35,
characterised in that the relative content of corticosteroids in the case of triamcinolone
or one of its derivatives, such as acetonide, is below 2 w-%, relative to total dry mass of
the drug-loaded carriers, even more preferably is below 1 w-% and most preferably is
25 below 0.5 w-%.

37. Formulation according to claim 35,
characterised in that the relative content of corticosteroids in the case of
hydrocortisone or one of its derivatives is below 20 w-%, relative to total dry mass of
30 the drug-loaded carriers, even more preferably is below 12.5 w-% and most preferably is
below 5 w-%.

- 57 -

5

38. Formulation according to claim 35,
characterised in that the relative content of corticosteroids in the case of dexamethasone or one of its derivatives is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most preferably is below 5 w-%.

10

39. Formulation according to claim 35,
characterised in that the relative content of corticosteroids in the case of clobetasol or one of its derivatives, such as propionate is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most preferably is below 5 w-%.

15

40. Formulation according to claims 35 to 39,
characterised in that the content of said corticosteroid is below the saturation maximum, defined as the content of corticosteroid at which the corticosteroid begins to crystallise in or outside the carrier.

20

41. Formulation according to claims 1 through to 25 and 35 through to 38,
characterised in that in order to speed up drug action a permeation enhancer is added.

25

42. Formulation according to claim 41,
characterised in that the permeation enhancer is selected from 1-acyl-azacycloheptan-2-ones (azones), 1-acyl-glucosides, 1-acyl-polyoxyethylenes, 1-acyl-saccharides, 2-n-acyl-cyclohexanones, 2-n-acyl-1,3-dioxolanes (SEPA), 1,2,3-triacyl-glycerols, 1-alkanols, 1-alkanoic acids, 1-alkyl-acetates, 1-alkyl-amines, 1-alkyl-n-alkyl-polyoxyethylenes, 1-alkyl-alkylates, n-alkyl-beta-D-thioglucosides, 1-alkyl-glycerides, 1-alkyl-propyleneglycols, 1-alkyl-polyoxyethylenes, (1-alkyl)-2-pyrrolidones, alkyl-

30

- 58 -

5 acetoacetates, alkylene-glycols, alkyl-methyl-sulphoxides (alkyl-DMSO), alkyl-propionates, alkyl-sulphates, diacyl-succinates, diacyl-N,N-dimethylaminoacetates (DDAA), diacyl-N,N-dimethylaminoisopropionates (DDAIP), phenyl-alkyl-amines.

43. Formulation according to claim 42,

10 **characterised in that** the bulk concentration range of the used enhancers is up to and around 5 % for 1-capryl-propylene glycol, 6-10 % for 1-[2-(decylthio)ethyl] azacyclopentan-2-one (=HPE-101), < 10 % for 1-dodecanol, < 10 % for 1-dodecyl-azacycloheptan-2-one (=azone), in the range of 10 % for 2-n-nonyl-1,3-dioxolane (SEPA), < 10 % for 2-n-octylcyclohexanone, up to, and preferably around, up to 20 %
15 for DMSO, up to, and between 5 % and 40 % for ethanol, in the range of 10 % or higher for ethylene glycol, up to 30 % for ethyl acetate, 5-50 % for glycerol, up to 75 % for isopropanol, 1-20 % for isopropyl myristate, between 1 and 20 % for oleic acid and oleyl-alcohol, of the order of around 1 % for oleyl-polyoxyethylene-ether, at least 10 % for propylene glycol.

20

44. Formulation according to claims 11 through to 25 and 35 through to 43,
characterised in that said corticosteroid is added in an amount which enables the formulation to be applied corresponding to an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between 0.1 mg cm^{-2} and 15 mg cm^{-2} , more
25 preferably between 0.5 mg cm^{-2} and 10 mg cm^{-2} , particularly preferably between 0.75 mg cm^{-2} and 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2} , if said corticosteroid is desired to exert a therapeutic effect in the deep subcutaneous, e.g. muscle or joints, tissue or else in the remote tissues, including the whole body.

30

5 45. Formulation according to claims 11 through to 25 and 35 through to 43,
characterised in that said corticosteroid is added in an amount which enables the
formulation to be applied with an area dose, as expressed by the total dry mass of
penetrant applied per unit area, of 1 between $\mu\text{g cm}^{-2}$ and $250 \mu\text{g cm}^{-2}$, more preferably
between 2.5 and $100 \mu\text{g cm}^{-2}$, even more preferably between $5 \mu\text{g cm}^{-2}$ and $50 \mu\text{g cm}^{-2}$
10 and most preferably between $7.5 \mu\text{g cm}^{-2}$ and $20 \mu\text{g cm}^{-2}$, if said corticosteroid is desired
to exert a mainly local, that is, superficial, rather than systemic therapeutic effect.

15 46. Formulation according to claims 11 through to 25 and 35 through to 45 ,
characterised in that consistency and, if necessary other characteristics of the
formulation are appropriately selected to enable spraying, smearing, rolling or sponging
of the formulation on the application area in particular by using a sprayer, spender,
roller or sponge, as appropriate.

20 47. A method for non-invasive application of corticosteroids by means of
penetrants according to any one of the preceding claims,
characterised in that the area dose, as expressed by the total dry mass of penetrant
applied per unit area, is selected to be between 0.1 mg cm^{-2} and 15 mg cm^{-2} , preferably
between 0.5 mg cm^{-2} and 10 mg cm^{-2} , particularly preferably between 0.75 mg cm^{-2} and
 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2} , if said corticosteroid
25 is desired to exert a therapeutic effect in the deep subcutaneous, e.g. muscle or joints,
tissue or else in the remote tissues, including the whole body.

30 48. A method for non-invasive application of corticosteroids by means of
penetrants according to any one of the preceding claims,
characterised in that the area-dose, as expressed by the total dry mass of penetrants
applied per unit area, is between $1 \mu\text{g cm}^{-2}$ and $250 \mu\text{g cm}^{-2}$, preferably between $2.5 \mu\text{g}$

- 60 -

5 cm² and 100 µg cm⁻², more preferably between 5 µg cm⁻² and 50 µg cm⁻² and most preferably between 7.5 µg cm⁻² and 20 µg cm⁻², if said corticosteroid is desired to exert a mainly local, that is, superficial, rather than systemic therapeutic effect.

49. A method for non-invasive application of corticosteroids associated with
10 or encapsulated into said penetrants according to any one of the preceding claims, **characterised in that** the formulation is applied by spraying, smearing, rolling or sponging on the application area in particular by using a sprayer, spender, roller or sponge, as appropriate.

15 50. Use of a formulation in accordance with any one of the preceding claims for the treatment of inflammatory disease, dermatosis, kidney or liver failure, adrenal insufficiency, aspiration syndrome, Behcet syndrome, bites and stings, blood disorders, such as cold-haemagglutinin disease, haemolytic anemia, hypereosinophilia, hypoplastic anemia, macroglobulinaemia, trombocytopenic purpura, furthermore, for the
20 management of bone disorders, cerebral oedema, Cogan's syndrome, congenital adrenal hyperplasia, connective tissue disorders, such as lichen, lupus erythematosus, polymyalgia rheumatica, polymyositis and dermatomyositis, epilepsy, eye disorders, such as cataracts, Graves' ophthalmopathy, haemangioma, herpes infections, neuropathies, retinal vasculitis, scleritis, for some gastro-intestinal disorders, such as
25 inflammatory bowel disease, nausea and oesophageal damage, for hypercalcaemia, infections, e.g. of the eye (as in infections mononucleosis), for Kawasaki disease, myasthenia gravis, various pain syndromes, such as postherpetic neuralgia, for polyneuropathies, pancreatitis, in respiratory disorders, such as asthma, for the management of rheumatoid disease and osteoarthritis, rhinitis, sarcoidosis, skin
30 diseases, such as alopecia, eczema, erythema multiforme, lichen, pemphigus and

- 61 -

- 5 pemphigoid, psoriasis, pyoderma gangrenosum, urticaria, in case of thyroid and vascular disorders.